PATENT APPLICATION

Applicants : Michael W. Pantoliano et al.

Application No.: 10/659,000 Confirmation No.: 4943

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing Date : September 9, 2003

For : CRYSTAL STRUCTURE OF ANGIOTENSIN-

CONVERTING ENZYME-RELATED CARBOXYPEPTIDASE

Group Art Unit : 1645

Examiner : Not yet assigned

New York, New York November 9, 2004

Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450

TRANSMITTAL LETTER FOR INFORMATION DISCLOSURE STATEMENT

Sir:

Transmitted herewith are an Information Disclosure

Statement, Form PTO-1449, and copies of references cited therein in the above-identified application. This Statement is submitted:

- [] within three months of the application filing date;
- [X] more than three months from the application filing date but before the mailing date of the first Office Action on the merits.

In accordance with 37 C.F.R. § 1.97, submission of this Statement requires no fee. However, if for any reason a fee is due, the Director is hereby authorized to charge payment of any fees required in connection with this Information Disclosure Statement to Deposit Account No. 06-1075. A duplicate copy of this letter is transmitted herewith.

Respectfully submitted,

Michele A. Kercher

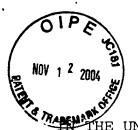
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Signature of Person Signing

Claire



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Sir:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97, applicants make the following references of record in the above-identified patent application:

¹ Applicants submit herewith Form PTO-1449, with the references listed therein. Applicants also provide copies of these references herewith.

References

Arndt et al., "Crystal Structure of a Novel Carboxypeptidase from the Hyperthermophilic Archaeon *Pyrococcus furiosus*," Structure 10:215-224 (2002).

Brown et al., "Structure of Neurolysin Reveals a Deep Channel that Limits Substrate Access," Proc. Natl. Acad. Sci. USA 98:3127-3132 (2001).

Christianson and Lipscomb, "Carboxypeptidase A," Acc. Chem. Res. 22:62-69 (1989).

Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry," J. Med. Chem. 33:883-894 (1990).

Crackower et al., "Angiotensin-Converting enzyme 2 is an Essential Regulator of Heart Function," Nature 417:822-828 (2002).

Dales et al., "Substrate-Based Design of the First Class of Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2) Inhibitors," J. Am. Chem. Soc. 124:11852-11853 (2002).

Danilczyk et al., "A Story of Two ACEs," J. Mol. Med. 81:227-234 (2003).

Donoghue et al., "A Novel Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9," Circ. Res. 87:e1-e9 (2000).

Ehlers et al., "Molecular Cloning of Human Testicular Angiotensin-Converting Enzyme: the Testis Isozyme is Identical to the C-Terminal Half of Endothelial Angiotensin-Converting Enzyme," Proc. Natl. Acad. Sci. USA 86:7741-7745 (1989).

Esther et al., "Mice Lacking Angiotensin-Converting Enzyme Have Low Blood Pressure, Renal Pathology, and Reduced Male Fertility," Lab Invest. 74:953-965 (1996).

Fernandez et al., "Angiotensin I-Converting Enzyme Transition State Stabilization by His¹⁰⁸⁹: Evidence for a Catalytic Mechanism Distinct from Other Gluzincin Metalloproteinases," *J. Biol. Chem.* 276:4998-5004 (2001).

Fülöp et al., "Prolyl Oligopeptidase: an Unusual β -Propeller Domain Regulates Proteolysis," Cell 94:161-170 (1998).

Gerstein et al., "Structural Mechanisms for Domain Movements in Proteins," *Biochemistry* 33:6739-6749 (1994).

Gerstein and Krebs, "A Database of Macromolecular Motions," Nucleic Acids Res. 26:4280-4290 (1998).

Grams et al., "Structure of Astacin With a Transition-State Analogue Inhibitor," Nature Struct. Biol. 3:671-675 (1996).

Groll et al., "Structure of 20S Proteasome from Yeast at 2.4 Å Resolution," Nature 386:463-464 (1997).

Holden et al., "Slow- and Fast-Binding Inhibitors of Thermolysin Display Different Modes of Binding: Crystallographic Analysis of Extended Phosphonamidate Transition-State Analogues," Biochemistry 26:8542-8553 (1987).

Holland et al., "Structural Comparison Suggests That Thermolysin and Related Neutral Proteases Undergo Hinge-Bending Motion During Catalysis," *Biochemistry* 31:11310-11316 (1992).

Inagami, "The Renin-Angiotensin System," Essays Biochem. 28:147-164 (1994).

Kim et al., "Crystal Structure of *Drosophila* Angiotensin I-Converting Enzyme Bound to Captopril and Lisinopril," *FEBS Letters* 538:65-70 (2003).

Kim and Lipscomb, "Comparison of the Structures of Three Carboxypeptidase A-Phosphonate Complexes Determined by X-Ray Crystallography," Biochemistry 30:8171-8180 (1991).

Knowles, "To Build an Enzyme...," Philos. Trans. R. Soc. London B332:115-121 (1991).

Kraut, "How Do Enzymes Work?" Science 242:533-540 (1988).

Krege et al., "Male-Female Differences in Fertility and Blood Pressure in ACE-Deficient Mice," Nature 375:146-148 (1995).

Liu et al., "Arg¹⁰⁹⁸ is Critical for the Chloride Dependence of Human Angiotensin I-Converting Enzyme C-domain Catalytic Activity," J. Biol. Chem. 276:33518-33525 (2001).

Matthews, "Structural Basis of the Action of Thermolysin and Related Zinc Peptidases," Acc. Chem. Res. 21:333-340 (1988).

Meng et al., "Automated Docking with Grid-Based Energy Evaluation," J. Comp. Chem. 13:505-524 (1992).

Natesh et al., "Crystal Structure of the Human Angiotensin-Converting Enzyme-Lisinopril Complex," *Nature* 421:551-554 (2003).

Navia and Murcko, "Use of Structural Information in Drug Design," Current Opinions in Structural Biology 2:202-210 (1992).

Oefner et al., "Structure of Human Neutral Endopeptidase (Neprilysin) Complexed with Phosphoramidon," J. Mol. Biol. 296:341-349 (2000).

Oudit et al., "The Role of ACE2 in Cardiovascular Physiology," Trends Cardiovasc. Med. 13:93-101 (2003).

Pantoliano et al., "Affinity Chromatographic Purification of Angiotensin Converting Enzyme," *Biochemistry* 23:1037-1042 (1984).

Patchett et al., "A New Class of Angiotensin-Converting Enzyme Inhibitors," Nature 288:280-283 (1980).

Pepine, "Potential Role of Angiotensin-Converting Enzyme Inhibition in Myocardial Ischemia and Current Clinical Trials," Clin. Cardiol. 20 (Suppl. II):II-58 - II-64 (1997).

Rawlings and Barrett, "Evolutionary Families of Metallopeptidases," Methods Enzymol. 248:183-228 (1995).

Rockel et al., "A Giant Protease with a Twist: The TPP II Complex from *Drosophila* Studied by Electron Microscopy," *EMBO* J. 21:5979-5984 (2002).

Scapin, "Structural Biology in Drug Design: Selective Protein Kinase Inhibitors," DDT 7:601-611 (2002).

Schechter and Berger, "On the Size of the Active Site in Proteases. I. Papain," *Biochem. Biophys. Res. Commun.* 27:157-162 (1967).

Shapiro and Riordan, "Inhibition of Angiotensin Converting Enzyme: Dependence on Chloride," *Biochemistry* 23:5234-5240 (1984).

Skeggs et al., "The Preparation and Function of the Hypertensin-Converting Enzyme," J. Exp. Med. 103:295-299 (1956).

Soubrier et al., "Two Putative Active Centers in Human Angiotensin I-Converting Enzyme Revealed by Molecular Cloning," Proc. Natl. Acad. Sci. USA 85:9386-9390 (1988).

Teague, "Implications of Protein Flexibility for Drug Discovery," Nature Rev. Drug Discovery 2:527-541 (2003).

Tipnis et al., "A Human Homolog of Angiotensin-Converting Enzyme: Cloning and Functional Expression as a Captopril-Insensitive Carboxypeptidase," J. Biol. Chem. 275:33238-33243 (2000).

Turner and Hooper, "The Angiotensin-Converting Enzyme Gene Family: Genomics and Pharmacology," Trends in Pharmacological Sci. 23:177-183 (2002).

Unno et al., "The Structure of the Mammalian 20S Proteasome at 2.75 Å Resolution," Structure 10:609-618 (2002).

Vickers et al., "Hydrolysis of Biological Peptides by Human Angiotensin-Converting Enzyme-Related Carboxypeptidase," J. Biol. Chem. 277:14838-14843 (2002).

Williams et al., "Identification of Two Active Site Residues in Human Angiotensin I-Converting Enzyme," J. Biol. Chem. 269:29430-29434 (1994).

Zhang et al., "Collectrin, a Collecting Duct-Specific Transmembrane Glycoprotein, Is a Novel Homolog of ACE2 and Is Developmentally Regulated in Embryonic Kidneys," J. Biol. Chem. 276:17132-17139 (2001).

Applicants respectfully request that the above-cited documents be (1) fully considered by the Examiner during the course of the examination of this application and (2) printed on any patent issuing from this application. Applicants also request that a copy of the enclosed Form PTO-1449, duly

initialed by the Examiner, be forwarded to the undersigned with the next official communication.

Applicants request favorable action in this application.

Respectfully submitted,

Michele A. Kercher

James F. Haley, Jr. (Reg. No. 27,794)
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Correspondence is being deposited with the U.S. Postal Service on First Class Mail in an envelope Addressed to:
Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 on

March

Signature of Person Signing

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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

ATTY. DOCKET NO. MNM/002	APPLN. NO. 10/659,000
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FILING DATE September 9, 2003	GROUP 1645

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS		G DATE IF OPRIATE
		FORE	IGN PATENT DOCUM	ENTS			
EXAMINER	DOCUMENT	DATE	COUNTRY	CLASS	SUBCLASS	TRAN	SLATION
INITIAL	NUMBER	DATE	COUNTRY	ULAGG	JUDICLASS	YES	NO
EXAMINER INITIAL	Arndt et al., "Crysta Pyrococcus furiosu	al Structure of s," Structure	lysin Reveals a Deep C	lase from the	e Hyperthermopl		
			rboxypeptidase A," Acc	. Chem. Res	s. 22:62-69 (1989	9).	
	Cohen et al., "Mole 33:883-894 (1990).		g Software and Method	ds for Medici	nal Chemistry," .	J. Med. C	hem.
	Crackower et al.,"A Nature 417:822-82		onverting enzyme 2 is a	an Essential	Regulator of Hea	art Function	on,"
			esign of the First Class tors," <i>J. Am. Chem.</i> So			nzyme-R	elated
	Danilczyk et al., "A	Story of Two	ACEs," J. Mol. Med. 8	1:227-234 (2	003).		

U.S. PATENT DOCUMENTS

EXAMINER

DATE CONSIDERED

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

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			tensin-Converting Enzy ensin 1-9," <i>Circ. Res.</i> 8			se (ACE2)		
	Ehlers et al., "Molecular Cloning of Human Testicular Angiotensin-Converting Enzyme: the Testis Isozyme is Identical to the C-Terminal Half of Endothelial Angiotensin-Converting Enzyme," <i>Proc. Natl Acad. Sci. USA</i> 86:7741-7745 (1989).							
,			iotensin-Converting Enz ertility," <i>Lab Invest</i> . 74:9			ure, Renal		
	Fernandez et al., "Angiotensin I-Converting Enzyme Transition State Stabilization by His ¹⁰⁸⁹ : Evidence for a Catalytic Mechanism Distinct from Other Gluzincin Metalloproteinases," <i>J. Biol. Chem.</i> 276:4998-5004 (2001).							
	Fülöp et al., "Prolyl 94:161-170 (1998).		se: an Unusual β-Prope	ller Domain	Regulates Prote	olysis," <i>Cell</i>		
	Gerstein et al., "Str 6749 (1994).	uctural Mecha	anisms for Domain Mov	ements in P	roteins," <i>Biochei</i>	mistry 33:6739-		
	Gerstein and Krebs (1998).	, "A Database	e of Macromolecular Mo	otions," <i>Nucl</i>	eic Acids Res. 2	6:4280-4290		
	Grams et al., "Struc 3:671-675 (1996).	ture of Astac	in With a Transition-Sta	te Analogue	Inhibitor," Natur	e Struct. Biol.		
	Groll et al., "Structu	re of 20S Pro	oteasome from Yeast at	2.4 Å Resol	ution," <i>Nature</i> 38	36:463-464 (1997).		
		alysis of Exte	inding Inhibitors of Ther ended Phosphonamidat					
	Holland et al., "Stru Undergo Hinge-Ber	ctural Compa nding Motion	arison Suggests That Th During Catalysis," <i>Biocl</i>	nermolysin a hemistry 31:	nd Related Neut 11310-11316 (19	ral Proteases 992).		

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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

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	Inagami, "The Renin-Angiotensin System," Essays Biochem. 28:147-164 (1994).							
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	Knowles, "To Build	an Enzyme	," Philos. Trans. R. Soc	. London B3	332:115-121 (199	91).		
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	Krege et al., "Male-Female Differences in Fertility and Blood Pressure in ACE-Deficient Mice," <i>Nature</i> 375:146-148 (1995).							
	Liu et al., "Arg ¹⁰⁹⁸ is C-domain Catalytic	Critical for the Activity," J. E	ne Chloride Dependence Biol. Chem. 276:33518-	e of Human 33525 (2001	Angiotensin I-Co).	nverting Enzyme		
	Matthews, "Structure Res. 21:333-340 (1		e Action of Thermolysir	and Relate	d Zinc Peptidase	es," Acc. Chem.		
	Meng et al., "Automated Docking with Grid-Based Energy Evaluation," <i>J. Comp. Chem.</i> 13:505-524 (1992). Natesh et al., "Crystal Structure of the Human Angiotensin-Converting Enzyme-Lisinopril Complex," <i>Nature</i> 421:551-554 (2003).							
	Navia and Murcko, "Use of Structural Information in Drug Design," Current Opinions in Structural Biology 2:202-210 (1992).							
			an Neutral Endopeptida 296:341-349 (2000).	se (Neprilysi	n) Complexed w	ith		
	Oudit et al., "The R (2003).	ole of ACE2 i	n Cardiovascular Physi	ology," <i>Tren</i>	ds Cardiovasc. I	Med. 13:93-101		

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	Pantoliano et al., "A Biochemistry 23:10		atographic Purification 34).	of Angiotens	sin Converting Er	nzyme,"	
	Patchett et al., "A N (1980).	lew Class of	Angiotensin-Converting	Enzyme Inh	nibitors," Nature 2	288:280-283	
			tensin-Converting Enzy rdiol. 20 (Suppl. II):II-58			schemia and	
	Rawlings and Barre (1995).	ett, "Evolution	ary Families of Metallo	peptidases,"	Methods Enzym	ol. 248:183-228	
	Rockel et al., "A Giant Protease with a Twist: The TPP II Complex from <i>Drosophila</i> Studied by Electron Microscopy," <i>EMBO J.</i> 21:5979-5984 (2002).						
	Scapin, "Structural Biology in Drug Design: Selective Protein Kinase Inhibitors," DDT 7:601-611 (2002).						
	Schechter and Berger, "On the Size of the Active Site in Proteases. I. Papain," <i>Biochem. Biophys. Res Commun.</i> 27:157-162 (1967).					nem. Biophys. Res.	
	Shapiro and Riordan, "Inhibition of Angiotensin Converting Enzyme: Dependence on Chloride," <i>Biochemistry</i> 23:5234-5240 (1984). Skeggs et al., "The Preparation and Function of the Hypertensin-Converting Enzyme," <i>J. Exp. Med.</i> 103:295-299 (1956).						
	Soubrier et al., "Two Putative Active Centers in Human Angiotensin I-Converting Enzyme Revealed by Molecular Cloning," <i>Proc. Natl. Acad. Sci. USA</i> 85:9386-9390 (1988).						
	Teague, "Implication (2003).	ons of Protein	Flexibility for Drug Disc	covery," <i>Natu</i>	ure Rev. Drug Di	scovery 2:527-541	
	Tipnis et al., "A Hui Expression as a Ca	man Homolog aptopril-Insen	g of Angiotensin-Conve sitive Carboxypeptidas	rting Enzyme e," <i>J. Biol. C</i>	e: Cloning and Finder. 275:33238	unctional -33243 (2000).	

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	Unno et al., "The S 618 (2002).	tructure of the	Mammalian 20S Prote	easome at 2.	75 Å Resolution,	" Structure 10:609-	
			ogical Peptides by Hum m. 277:14838-14843 (20		sin-Converting E	Enzyme-Related	
	Williams et al., "Identification of Two Active Site Residues in Human Angiotensin I-Converting Enzyme, J. Biol. Chem. 269:29430-29434 (1994).					onverting Enzyme,"	
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